LETTER TO THE EDITOR

A CASE WITH RARE TYPE OF CONGENITAL DISORDER OF GLYCOSYLATION: PGM1-CDG

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Congenital disorders of glycosylation (CDG) are a rapidly growing family of genetic diseases first reported in 1980 (11). They are caused by deficient glycosylation of glycoconjugates, such as N-linked glycoproteins, O-linked glycoproteinsand glycolipids. Some 60 CDG are actually known. Phosphoglucomutase 1 deficiency, first reported in 1963 (11), has only recently been identified as a CDG with a remarkably broad clinical presentation (5, 8, 12, 13). We report on another patient with this CDG.

A 19-months-old girl was admitted for evaluation of feeding difficulties and recurrent hypoglycemia that occurred almost every month. She was the third child of consanguineous healthy parents. There was no family history of similar symptoms. She showed a short stature, prominent forehead, small face, depressed nasal bridge, unilateral-median cleft palate/bifid uvula and hepatomegaly 5 cm below the costal margin. Her weight was 7.1 kg (SDS: -3), height was 66 cm (SDS: -3.97). Psychomotor development and neurological examination were normal. There was epiphora due to lacrimal duct obstruction. Routine laboratory investigations showed normal blood count, routine urine analysis and serum creatinine, total lipids, total LDL- and HDL-cholesterol, ammonia, creatine phosphokinase, acylcarnitines, amino acids, thyroid hormones, biotinidase activity and urine organic acids and sugar chromatography. Serum transaminases were increased [AST: 291U/L, ALT: 109U/L (nl: 0-40)]. Ultrasonographic examination showed enlarged liver size with normal echogenity. Echocardiography and brain (including hypophysis) magnetic resonance imaging were normal. During follow-up hypoinsulinemic hypoglycemia (39 mg/dl) was detected with increased serum cortisol, adrenocorticotropic hormone, growth hormone, and normal metabolic screening tests (urine glucose and organic acids, and serum lactic acid, ammonia, bicarbonate, amino acids

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and acylcarnitine levels. Serum insulin like growth factor 1 (IGF1) was low 16.15 ng/ml (nl: 55-110), but showed a normal response to growth hormone. Insulin like growth factor binding protein 3 (IGFBP3) was 578 ng/ml (nl: 2450-3500). Growth hormone therapy was nevertheless started but hypoglycemia attacks continued and therefore this therapy was stopped. Serum thyroxine binding globuline was low [5 µcg/ml (29-54)]. Partial thromboplastin time was 41.8 (nl: 18-28) and prothrombin time was 19.3 seconds (nl: 10-14) factor X 45 % (50-150), factor VII 15.8 % (50-150), FXI 15 % (50-150), antithrombin III 10 % (80-120), protein C 5 %(70-130), and protein S 8 % (65-140). On follow-up, cardiomyopathy developed and serum was found increased.

Serum transferrin IEF showed a type 2 pattern. On MALDI-TOF analysis of serum transferin there was an aglycan and a monoglycan transferin species besides the normal diglycan transferin. On the basis of these results and clinical features, mutation analysis of the PGM1 gene was performed by direct sequencing of this 11 exons. A homozygous mutation was found: c.551delT (p.F184Sfs*9) and the parents were heterozygous for this mutation.

Phosphoglucomutase (PGM) comprises three isoenzymes with different tissue distribution (PGM1, PGM2 and PGM3). PGM1 is expressed ubiquitously and accounts for 80-90 % of the total PGM activity in most tissues (4, 7). It catalyses the bidirectional interconversion of glucose 1-phosphate and glucose 6-phosphate, and is thus on the crossroad between glycolysis/glucose production and glycogen metabolism/UDP-galactose synthesis.

PGM1 deficiency has first been reported half a century ago (11). Since then a few patients have been described including, in 2009, an adult with exercise-induced muscle cramps, episodic rhabdomyolysis, and muscular glycogen storage (‘glycogenesis XIV’) (5, 8, 12, 13). Only in 2012, the full clinical presentation of PGM1 deficiency was recognized comprising bifid uvula/cleft palate, hepatophy with decreased coagulation factors, growth retardation (with normal or increased growth hormone levels), myopathy, dilated cardiomyopathy, hypoglycemia, and, less frequently, low serum TSH, ACTH and hypogonadotrophic hypogonadism (5). The absence of neurological symptoms can be explained by the presence of PGM2 (3) and phosphomannomutase 1 (6) in brain. Moreover, at the same time PGM1 deficiency was identified as a glycosylation disorder with, on the one hand, a type 2 pattern on serum TfIEF, pointing to a glycan remodeling defect (Golgi defect) and, on the other hand, a loss of complete glycans on mass spectrometry of intact Tf. The latter points to a glycan assembly defect (ER/pre-ER defect). Using the current CDG nomenclature (2) this disease should

be called PGM1-CDG. This dual glycosylation defect (CDG-I/II) was only reported in galactosemia (9). In both disorders there is an accumulation of galactose 1-phosphate, probably inhibiting (by competion ?) the galactosylation of glycoproteins in the Golgi apparatus, while in PGM1-CDG there is shortage of the galactose donor UDP-galactose. Galactose administration should be beneficial to these patients. Recently a paper, which has been published by Tegtmeyer *et al.*, include phenotypic features of patients diagnosed PGM-1 CDG. In this report has been mentioned that, supplementation with galactose leads to biochemical improvement in patients (10).
In conclusion, PGM1-CDG broadens the already very broad phenotypic spectrum of CDG.

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